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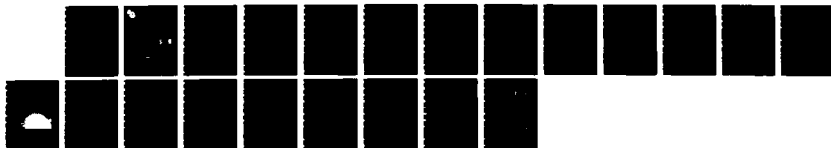
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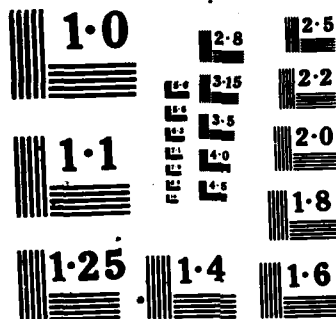
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**LABORATORY NOTE NO. 86-59**

## PERMANENT VISUAL CHANGE ASSOCIATED WITH PUNCTATE FOVEAL LESIONS

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Permanent Visual Change Associated with Punctate Foveal Lesions  
---Zwick, Bloom, Beatrice

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*Edum S. Beatrice* 7 Mar 66  
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## Permanent Visual Change Associated with Punctate Foveal Lesions

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### SUMMARY

In order to understand battlefield hazards of laser exposure under field conditions, it has been necessary to evaluate effects of small, punctate foveal lesions on visual function of non-human primates. Previous experiments have found a correlation between functional loss and foveal damage. The present investigation has found that the ability to detect the effects of small foveal lesions, those that might be produced under field conditions, is not an easy task. The possibility that considerable foveal damage could actually occur before a measurable change in visual function could be detected with presently available visual function testing procedures is raised by the results of this investigation. Recommendations for more sensitive visual function test procedures have been offered.

Normal human vision is an integral part of any specific combat scenario. Protection of the human visual sensor, as well as a thorough understanding of how noxious combat exposure conditions might alter its function, is essential to the success of any military mission.

In recent years, the combat threat from directed energy sources has become increasingly obvious. Laser range finders, laser designators, and potential laser weapons all pose a unique hazard to the human eye. For this reason, knowledge of how various modes of light exposure can affect vision, the mechanism of photic damage and recovery that the visual system can mediate, and development of clinical test apparatus for early and preventative ocular medical treatment have become critical mission necessities.

For many years, retinal lesions produced by intense light exposure were thought to result, primarily, from thermal changes produced at the retina, although some early work had suggested a non-thermal damage component (1,2). Recent investigations of acute intense light exposure have revealed that photically induced retinal lesions could be produced by non-thermal as well as by thermal mechanisms of light damage (3,4,5,6,7). Other investigations of a slightly different type, where the effects of prolonged exposure to environmental light levels were investigated, had suggested that night visual function might be transiently impaired following prolonged exposure to bright

environmental lighting conditions(8,9). More recently, animal investigations have demonstrated that chronic exposure to visible spectral light at levels not capable of producing thermal retinal changes can cause significant alteration of the color vision photoreceptor mechanisms (6,10). Changes in spectral sensitivity for increment threshold criteria, for visual acuity criteria, and for retinal electrophysiological criteria have been observed following such exposure (4,6,10,11).

With the development of laser sources, at least a third potential damage modality of light on the visual system was created. The ability to Q-switch a laser source to produce pulses as short as 2-20 nsec has been theorized to create effects that may involve acoustic/mechanical shock. For visible wavelengths, Q-switched pulses may involve all three damage modalities.

Investigations of Q-switched laser exposure effects have typically concentrated on large foveal exposure areas at levels that always produced gross foveal damage (4). In such experiments long-term effects on visual acuity and spectral visual function have been reported (4,12). Total foveal damage results in acuity changes from 20/20 Snellen acuity to 20/200 Snellen acuity. After several weeks such changes usually have been reduced to levels more consistent with expected foveal acuity loss, had only the central foveola been damaged. This initial disproportionate acuity deficit has been postulated to result from the edematous process associated with such a severe retinal injury (4,13). While the abatement of the edema may take several weeks, continued recovery of function over several months has been reported (4). The explanation of such recovery may reside in observations made by T'so (13), who found that gross morphological photic damage to the macula of the rhesus monkey abated over several months post-exposure. Animals sacrificed at six months post-exposure showed near normal foveal macular areas as compared to animals sacrificed earlier. T'so suggested that in the course of post-exposure recovery, photoreceptors adjacent to damaged photoreceptors slide into areas originally occupied by the damaged receptors, filling in the foveal retinal receptor mosaic. This finding may explain how overall acuity can recover while spectral sensitivity for the fovea remains altered (12); new cones may provide the resolution mosaic necessary for acuity, but because of different absorption spectra, alter the overall spectral sensitivity of the fovea itself.

Several recent experiments (4,14) have suggested that acute exposures can have non-thermal components, especially at energy levels determined for the transition zone from temporary to permanent visual function change. It is possible that such foveal retinal damage mechanisms could not be elucidated in studies similar to those mentioned above, where the entire foveal region has undergone gross damage. Furthermore, in most of the investigations where suprathreshold exposures were made, the exposures were placed under

anesthesia, eliminating the possibility of examining the immediate, transient alteration of visual function. Measurements were only obtainable two to three days post-exposure.

Small spot, Q-switched, repetitively pulsed laser exposures represent a realistic hazard. Such exposure can occur with present day laser systems, either in training or in combat. The above studies presently can not resolve the immediate effects of such exposure on vision. In the present experiment we have sought to examine the effects of small spot laser exposures that were placed on the fovea by behavioral procedures. We have studied the rhesus contrast sensitivity function to determine how such exposures might alter spatial visual function for both transient and long-term observations.

#### METHOD

The optical system used in this experiment is shown in Figure 1. The raw beam from a frequency-doubled neodymium laser source (532 nm) operating at 20 HZ was made coaxial with the gap in a Landolt ring acuity target subtending  $<1$  min of arc (20/20 Snellen acuity). Exposure consisted of six 20 nsec pulses delivered within a 300 msec time window. The nominal Total Intraocular Energy (TIE) per pulse for a 3 mm pupil, averaged 1-3 uJoules. This energy level is within the threshold region for producing minimal ophthalmoscopically visible retinal burns. Due to the parallel nature of the beam, exposure resulted in diffraction limited retinal spots (20-50 microns).

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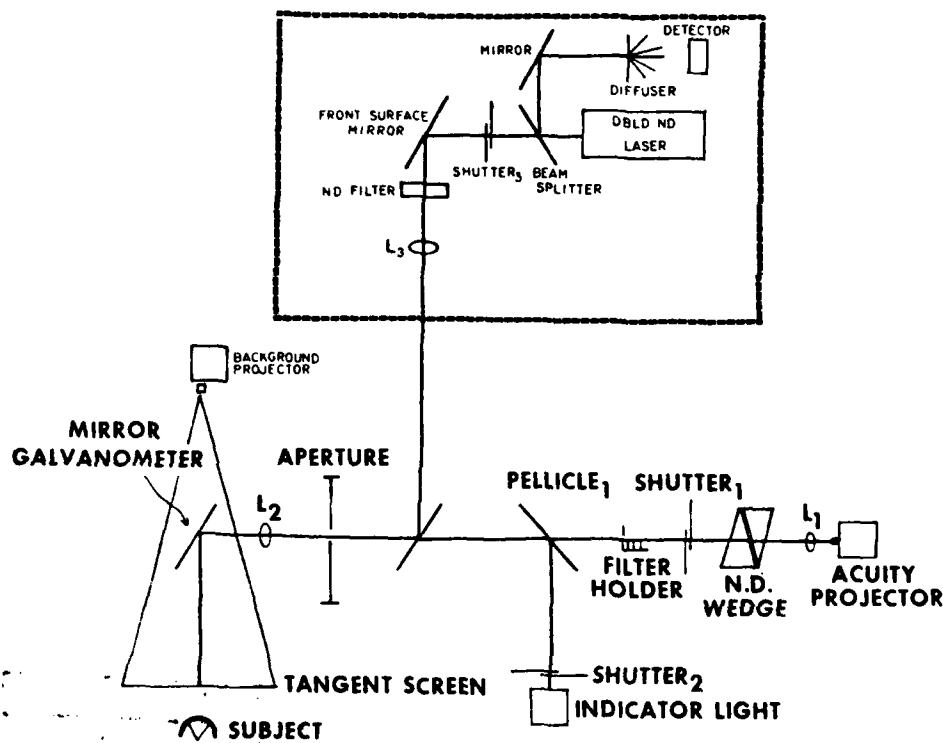


Figure 1. Alterations in contrast sensitivity were examined following exposures to a Q-switched frequency-doubled neodymium laser (532 nm) operated at a 20 Hertz pulse repetition frequency. The optical design allowed for placement of the laser beam coaxial with a 0.75 min arc gap in a Landolt ring, producing diffraction limited (50 micron) retinal exposures.



Landolt rings ("C's") and rings without gaps ("O's") were projected onto a ground glass rear projection screen located about 0.5 meters directly in front of the rhesus monkey. All of the stimuli were negative contrast achromatic (white figure on a dark background) targets so that an independent light source could serve as a background contrast channel. Because the luminance of the background channel was additive with the target luminance, the contrast ratio was defined as the luminance of the test plus the background, minus the background, divided by the sum of the luminance of the test plus two times the background  $(T+B)-B/T+2(B)$ . Contrast sensitivity was defined as the reciprocal of the contrast ratio required at threshold for accurate discrimination of the acuity stimuli. The gap size of the Landolt rings and gapless rings varied from 7 to 14 min of arc (38.5 cycles/deg to 2.2 cycles per degree).

Four rhesus monkeys (*Macaca mulatta*) were trained on a Landolt ring visual acuity task (12,14,15) in which exposure to a laser flash could be administered during task performance (4,14). Training required 6 to 9 months for each animal to successfully discriminate Landolt rings from gapless rings and several additional months for stable threshold acuity measurements in each animal. Briefly, this behavioral procedure required that a response lever be depressed and held down by the animal for a variable period of about 3 seconds following the presentation of a small white spot of light. The acuity target (either a Landolt ring or a gapless ring) would then be presented for 500 msec on the rear-projection tangent screen facing the animal. If the animal released the response lever only following the offset of the acuity target, two additional response panels were illuminated, displaying a Landolt ring and a gapless ring. Positive reinforcement (fruit juice) required that the animal depress the correct panel, matching the stimulus target presented. Correct delayed, forced-choice matching responses caused subsequent targets to be presented at reduced contrast levels, while incorrect responses resulted in increased target contrast on the next trial. Target contrast was controlled by the use of circular neutral density wedges. All animals had pretraining refractive errors of less than 1/2 diopter; all had normal appearing retinal fundi prior to exposure. Reexamination of any given animal's retina was generally given after all its exposures had been completed.

Contrast sensitivity for Landolt ring test stimuli was determined by an up-and-down visual tracking procedure (4,12,14,15), allowing rapid determination of threshold. Animals were trained to yield highly stable baselines with minimal variation across sessions. A stability criterion of approximately 0.2 to 0.4 log units in contrast, maintained over a 30 to 60-minute period for several sessions was generally required before the animal was placed in the exposure paradigm. The effect of laser exposure on contrast sensitivity was determined for one spatial frequency each session, as long as post-exposure measurements on the tested spatial frequency returned to its

previously determined session baseline levels. Contrast sensitivity measurements over the entire spatial frequency spectrum were made periodically between exposure sessions to determine long-term changes not observable in the daily exposure sessions.

## RESULTS

Recovery of contrast sensitivity following laser exposure for a large target (20/267 or 2.2 cycles/ degree) and a small target (20/15 or 38.5 cycles/deg) is shown in Figure 2. The ordinate represents the percent deficit of postexposure sensitivity relative to the sessions baseline sensitivity prior to exposure. Sensitivity averaged over 2 - minute blocks following exposure shows similar transient changes for large and small targets, both in maximum deficit and time course of recovery to baseline. Figure 2 shows recovery functions for a single animal, however the results are representative of the transient deficits observed for all subjects.

Data derived from recovery curves as seen in Figure 2, for each of the four animals shows that recovery time is nearly uniform across the spatial frequency spectrum. Mean contrast sensitivity at 2,6, and 16 minutes postexposure, across all exposure sessions for each spatial frequency is shown in Figure 3. For each of the four animals, the decrease in contrast sensitivity appears to be uniform across spatial frequencies. Both small and large targets showed little recovery during the first 2 to 4 minutes postexposure. After the initial 4 minutes postexposure, recovery was evident, with return to baseline by 16 minutes.

Repeated exposure trials had no initially observable long-term effects on contrast sensitivity. However, after several months differences in the slopes of the post-exposure contrast sensitivity functions became evident (Figure 4) for three of the four animals tested. The change in slope was a steepening due to an increase in the contrast sensitivity for the larger spatial frequencies, while sensitivity for the finer frequencies showed minimal change. In one of these animals (S3), exposure was continued until contrast sensitivity was no longer obtainable at the finest spatial frequency. Full spectrum sensitivity measured after this loss of foveal function (Figure 5) revealed a more shallow slope for the contrast sensitivity curve, approximating that of the preexposure function. Coincident with the loss of fine spatial frequency sensitivity there was a return to preexposure level for sensitivity measured for the largest spatial frequency targets.

Fundus observations of animals examined after the completion of all laser exposure sessions revealed small punctate lesions in the foveal areas including the foveola. A representative fundus photograph of such a retina is shown in Figure 6.

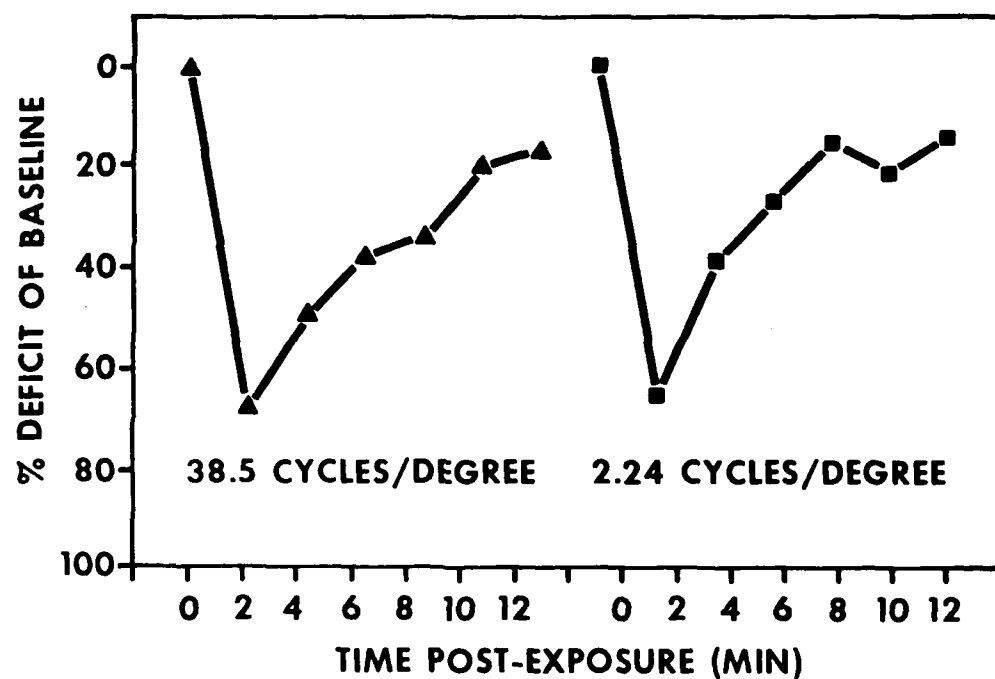


Figure 2. Sample recovery of contrast sensitivity following laser exposure. Contrast sensitivity measured for a large target (2.24 cycles/degree) and a small target (38.5 cycles/degree) is plotted as the percent deficit of post-exposure sensitivity relative to that session's preexposure baseline. Sensitivity following exposure shows similar transient changes both in maximum deficit and the time course of recovery to baseline.

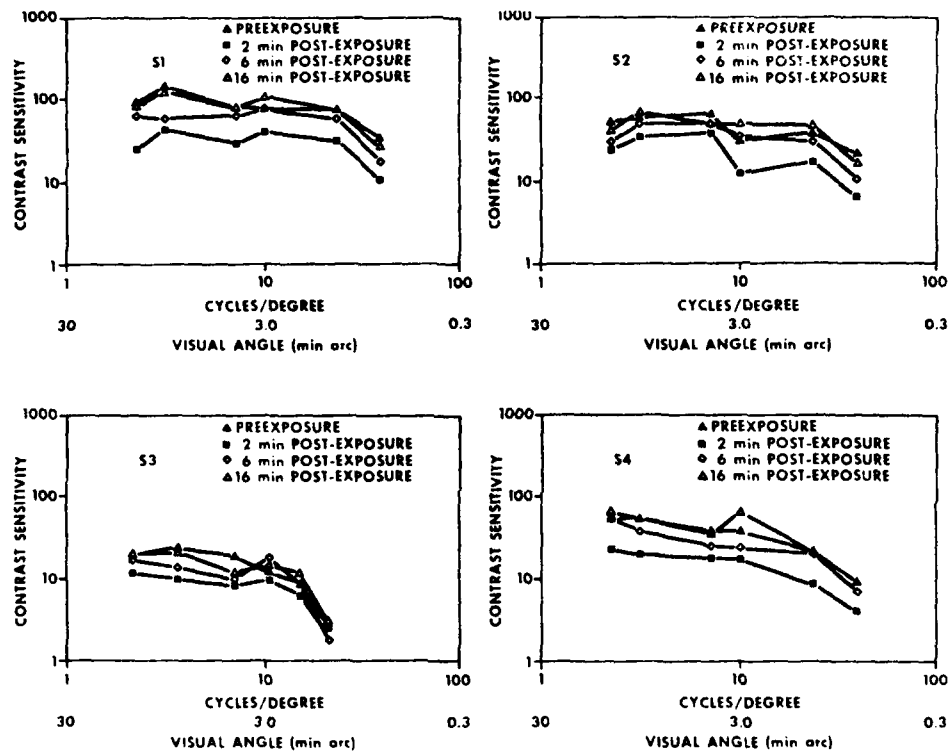


Figure 3. Data derived from recovery curves was used to examine the transient effects of laser exposure across the spatial frequency spectrum from 2.24 to 38.5 cycles/degree. This frequency range corresponds to an angular subtense of 14 to 0.75 min arc for the gap in the Landolt ring targets. For all animals, contrast sensitivity over the first 2 minutes following exposure was uniformly depressed across the spatial frequency spectrum. While full recovery was evident in most cases by 16 minutes, recovery for the mid-range spatial frequencies appeared to be more rapid than that observed for the low and high spatial frequency targets.

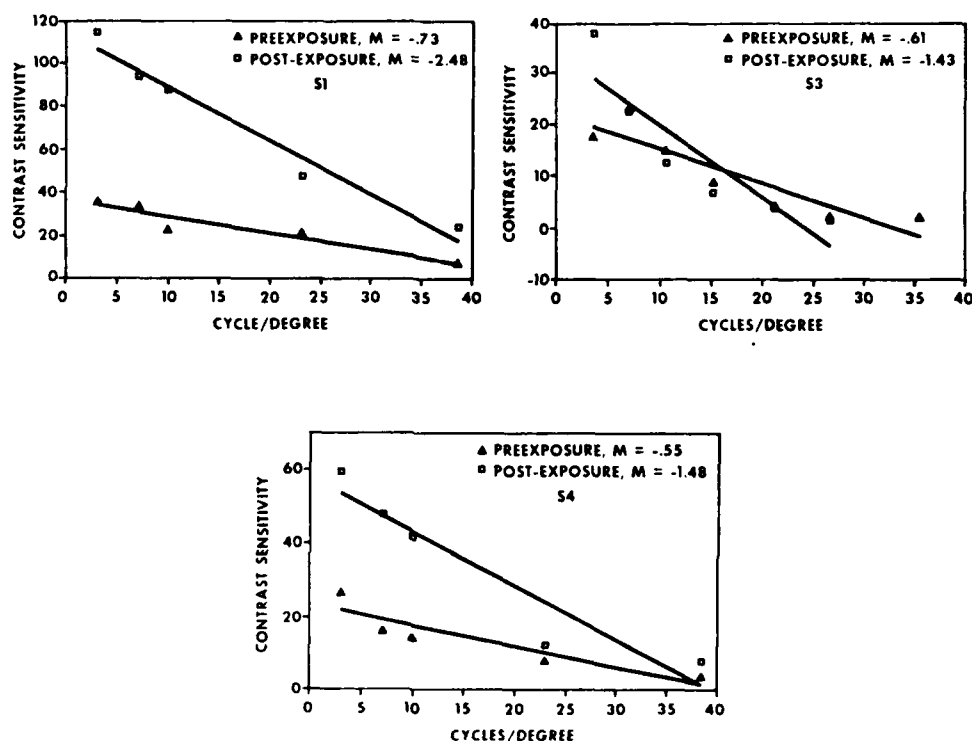


Figure 4. Long-term effects of small spot lesions were not readily apparent following daily exposures. Recovery to preexposure contrast sensitivity usually occurred within the same session. Examination of the full spectrum contrast sensitivity function after cumulative exposure sessions, compared to similar functions obtained prior to any exposures, revealed a steepening in the slope of the post-exposure function, as determined by a linear regression using the Least Squares Fit method. This steepening involved an increase in contrast sensitivity for the lower spatial frequencies with minimal change for the finer test targets.

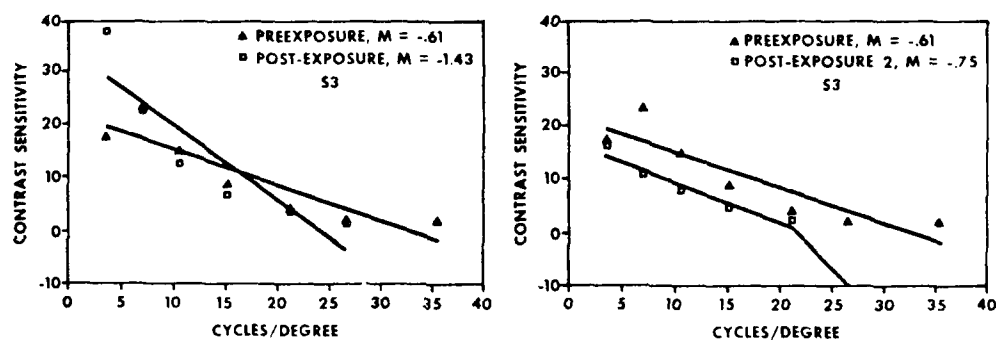


Figure 5. Cumulative foveal exposure was continued for one animal (S3) until a permanent high frequency loss was evidenced by the inability to obtain contrast thresholds for the smaller acuity targets. When this deficit occurred, sensitivity for the low spatial frequency targets returned to normal levels. A slightly steeper slope (-0.75) for the post-exposure 2 function results from the decrease in high frequency contrast sensitivity.



Figure 6. Fundus observations of animals examined after the completion of all laser exposures revealed small punctate lesions in the foveal region, including the foveola. The fundus photograph above, taken from one of the animals, shows the central pattern of lesions consistent in size with minimal spot retinal exposures.

## DISCUSSION

The transient changes in sensitivity obtained for exposure conditions used in this experiment differ considerably from those obtained in experiments where foveal damage was more complete or where exposure duration was considerably longer (100 msec). In experiments where foveal damage was more complete, long-term changes in achromatic acuity were measurable as long as six to nine months post-exposure, and where acuity recovery had been obtained, spectral acuity and sensitivity measurements still revealed a basic change in foveal function (10). In investigations where longer pulse widths (100 msec) and spot sizes from 50 to 350 microns were used, a transition level between permanent visual change and transient visual change was typically found, although smaller spot exposures did require higher transition level exposure energies (4).

More than one experimental factor may be responsible for the present results. The current experiment dealt with irradiation spot sizes of about 50 microns compared to spot sizes varying between 500 and 1000 microns used in previous Q-switched exposure experiments of the present type. The transient effects observed here may reflect similar damage processes observed with larger spot size exposures, but related to a more limited area of foveal damage. Transient recovery functions might reflect the spread of local edema from the exposure site and the subsequent reduction in its local opacity.

Following such possible edema abatement, a sufficient number of foveal photoreceptors may initially still be available to mediate normal spatial vision processes, even though photoreceptor damage has occurred. With continued exposure, as was the case here, a sufficient number of foveal photoreceptors may eventually become damaged producing the observed alteration in the slope of the contrast sensitivity function. The elevation in sensitivity for the larger gap sizes may reflect foveal cone damage manifested by a disinhibition of the normal lateral inhibitory influence of foveal cones on parafoveal receptor systems; alternatively it may reflect more parafoveal involvement in the contrast sensitivity measurement as foveal photoreceptors are gradually damaged. As exposure continues, more spatially spread out damage may produce a permanent reduction in sensitivity, generalized over much of the spatial frequency spectrum. Furthermore, fine tuning of the retinal mosaic by local receptor alignment adjustments might serve as the mechanism for masking initial loss in fine acuity (16,17). Morphological evidence for such mechanisms has been reported for rodent and primate photoreceptors (18,19,20,21).

The wavelength of the laser source (532 nm) is another factor that differs from previous experiments using Q-switched exposures. All previous experiments involved laser wavelengths either in the near infrared (1060nm) or long wavelength region (694 nm). The wavelength



used in the present experiment is very close to the peak of the photopic sensitivity function (550 nm) and uniquely situated with respect to the absorption maxima of the two long wavelength cone pigments (520 and 575 nm). Thus, efficiency of such Q-switched exposure to alter visual processes either transiently or permanently should not be overlooked. While edema may contribute to the short-term change in function, photochemical damage processes found in many other experiments may account for the longer term changes in contrast sensitivity. Even transient changes may result from cone photoreception of 532 nm quanta, inducing neural spread due to receptor overload. The failure to observe more obvious permanent change may simply reflect our use of achromatic acuity targets. In experiments supporting photochemical photoreceptor damage mechanisms, spectral test stimuli were always employed (4,6,10). Use of spectral test stimuli show that more permanent effects are either revealed or reflected earlier for such measures of visual function (4).

Finally, the pulse parameters for this experiment differed from previous experiments. In this experiment Q-switched pulses were delivered in a pulse train. While no previous functional work has been done with Q-switched pulse trains of visible light, morphological investigations involving threshold determinations for retinal burn suggest that such thresholds are lower than those obtained with single Q-switched pulses (22,23). Such pulse additivity might also contribute to the transient effect, as early work in our laboratory with single Q-switched pulse exposure often produced effects that were delayed by periods of time up to 60 seconds. More recent electrophysiological work confirms these findings (24). A single minimal spot Q-switched pulse may be capable of producing retinal damage, but still may be insufficient in signalling the initial visual event involved in quantal absorption by the photoreceptor chromophore. But when Q-switched pulses are presented together in a train of pulses lasting several hundred milliseconds, the visual event may be appropriately signaled to the neural retina.

Thus, while gross foveal damage from large spot, Q-switched laser sources would provide an obvious clinical signal that vision has been altered, small spot exposure might not provide as obvious a signal. Furthermore, as many present military rangefinders and designators involve non-visible wavelengths, retinal damage could occur without any obvious change in vision.

Novel military clinical visual function tests may be required for detection of retinal injury. Measures of visual acuity, alone, would not show the inhibitory/disinhibitory nature of retinal alteration as seen by the slope changes in contrast sensitivity reported in the present experiment. Conventional sine wave grating contrast sensitivity measurements may also be insufficient, as they are designed to treat the retinal surface as a detector with uniform sensitivity. Clinical tests that measure both spectral and spatial

resolution under threshold contrast conditions represent the most sensitive kinds of visual function tests capable of early preventative diagnosis. As training and combat requirements involve ever increasing usage of directed energy devices, the development and evolution of appropriate visual function tests must be given the highest priority.

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1. REPORT NUMBER Laboratory Note No. 86-59	2. GOVT ACCESSION NO.	3. RECIPIENT'S CATALOG NUMBER
4. TITLE (and Subtitle) PERMANENT VISUAL CHANGE ASSOCIATED WITH PUNCTATE FOVEAL LESIONS		5. TYPE OF REPORT & PERIOD COVERED
		6. PERFORMING ORG. REPORT NUMBER
7. AUTHOR(s) Harry Zwick, PhD; Kenneth R. Bloom, BA; Edwin S. Beatrice, COL, MC		8. CONTRACT OR GRANT NUMBER(s)
9. PERFORMING ORGANIZATION NAME AND ADDRESS Letterman Army Institute of Research Division of Ocular Hazards Presidio of San Francisco, CA 94129-6800		10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS WU 245, Physiologic Basis of Laser Effects, 3M161102BS10 Task: CF
11. CONTROLLING OFFICE NAME AND ADDRESS US Army Medical Research & Development Command Fort Detrick Frederick, MD 21701		12. REPORT DATE
		13. NUMBER OF PAGES
14. MONITORING AGENCY NAME & ADDRESS (if different from Controlling Office)		15. SECURITY CLASS. (of this report) Unclassified
		15a. DECLASSIFICATION/DOWNGRADING SCHEDULE
16. DISTRIBUTION STATEMENT (of this Report) This document has been approved for public release and sale: distribution is unlimited.		
17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)		
18. SUPPLEMENTARY NOTES		
19. KEY WORDS (Continue on reverse side if necessary and identify by block number) Laser; Visual function; Pulsed; Rhesus; Punctate lesions; Fovea; Contrast sensitivity.		
20. ABSTRACT (Continue on reverse side if necessary and identify by block number) In order to understand battlefield hazards of laser exposure under field condi- tions, it has been necessary to evaluate effects of small punctate foveal lesions on visual function of non-human primates. Previous experiments have found a correlation between functional loss and foveal damage. The present investigation showed that detecting the effects of small foveal lesions - those that might be produced under field conditions - is not an easy task. From the results of this investigation, we foresee the possibility that considerable foveal damage could occur before a measurable change in visual function could be detected with.		

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Abstract cont.

presently available visual function testing procedures. We recommend more sensitive visual function test procedures, such as clinical tests that measure both spectral and spatial resolution under threshold contrast conditions.

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